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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,839	KAELIN, WILLIAM G.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,8,11,13 and 16-36* is/are pending in the application.

4a) Of the above claim(s) *16-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8,11 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *August 25, 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on November 28, 2007 is acknowledged.

Applicant has elected the invention of Group I, claim(s) 1-15, drawn to a transgenic mammal comprising a recombinant nucleic acid molecule stably integrated into the genome of said mammal, said recombinant nucleic acid molecule comprising an E2F responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein, and a method for the production of said transgenic mammal.

Within Group I, Applicant has elected the following species, wherein:

i) the transgenic mammal is a mouse,

ii) the E2F-responsive promoter binds E2F1,

iii) the promoter is an E2F1 promoter,

iv) the bioluminescent protein is a luciferase, and

v) the host cell from which to make a transgenic animal is an embryonic cell.

Upon further review and consideration of the claimed subject matter, the Examiner rejoins the "egg cell" as a species from which to make a transgenic animal.

Amendments

Applicant's response and amendments, filed August 25, 2009, to the prior Office Action is acknowledged. Applicant has cancelled Claims 3, 7, 9-10, 12 and 14-15, withdrawn Claims 16-34, amended Claims 1-2, 4-6, 8, 11 and 13, and added new claims, Claims 35-36.

Claims 35-36 are drawn to non-elected E2F promoter species. Applicant is respectfully reminded of the species election requirement set forth in the Office Action mailed June 28, 2007.

Claims 16-36 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1-2, 4-6, 8, 11 and 13 are under consideration.

Priority

This application is a 371 of PCT/US03/35282 filed on November 4, 2003. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/423,673, filed on November 4, 2002 under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Response to Amendment

The Examiner acknowledges Applicant's amendment to the Specification to make specific reference to the prior-filed application in compliance with 37 CFR 1.78(a).

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on August 25, 2009 that has been considered. The signed and initialed PTO Forms 1449 are mailed with this action.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the August 25, 2009 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

1. **The prior objection to the disclosure is withdrawn** in light of Applicant's amendment to the Specification to properly demarcate trademarks.

2. **The prior objection to the specification as failing to provide proper antecedent basis for the claimed subject matter is withdrawn** in light of Applicant's cancellation of Claims 7 and 9.

Claim Rejections - 35 USC § 101

3. **The prior rejection of Claims 1-9, 11 and 13 under 35 U.S.C. 101 is withdrawn** in light of Applicant's amendment to the claims limiting the scope of the claims to a transgenic mouse.

Claim Rejections - 35 USC § 112

4. **The prior rejection of Claims 7-9 under 35 U.S.C. 112, second paragraph, is withdrawn** in light of Applicant's amendment to the claims.

5. **The prior rejection of Claims 1, 6-10 and 13-15 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn** in light of Applicant's amendment to the claims.

6. **The prior rejection of Claims 1-9, 11 and 13-14 under 35 U.S.C. 112, first paragraph, is withdrawn** in light of Applicant's amendment to the claims limiting the scope of the claims to a transgenic mouse.

Claim Rejections - 35 USC § 102

7. **The prior rejection of Claims 1-2, 7-11 and 13-15 under 35 U.S.C. 102(b)** as being anticipated by Muller et al (Mol. Cell. Biol. 20(9):3316-3329, 2000), as evidenced by Muller et al (J. Biol. Chem. 274(16):11220-11228, 1999) **is withdrawn** in light of Applicant's amendment to the claims to recite a subgenus of E2F-responsive promoters, none of which Muller (2000) teach.

8. **Claims 1-2, 4, 6, 8, 11 and 13 stand rejected under 35 U.S.C. 102(e)** as being anticipated by Holland (U.S. Patent 7,041,869, provisional application filed October 4, 2002), as evidenced by GenBank Accession AF516106.1, GI:21326179.

The Ariniello Declaration filed on August 25, 2009 under 37 CFR 1.131 has been considered but is ineffective to overcome the Holland reference.

The Holland reference is a U.S. patent or U.S. patent application publication of a pending or patented application that claims the rejected invention. Specifically, the species of the E2F-promoter is a claimed species in both Holland and the present application.

An affidavit or declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable invention, see MPEP § 2306. If the reference and this application are not commonly owned, the reference can only be overcome by establishing priority of invention through interference proceedings. See MPEP Chapter 2300 for information on initiating interference proceedings. If the reference and this application are commonly owned, the reference may be disqualified as prior art by an affidavit or declaration under 37 CFR 1.130. See MPEP §718.

Holland claims a transgenic mouse whose genome comprises an E2F1 promoter operably linked to a luciferase reporter protein.

Claim Rejections - 35 USC § 103

9. **The prior rejection of Claims 4-6 under 35 U.S.C. 103(a)** as being unpatentable over Muller et al (Mol. Cell. Biol. 20(9):3316-3329, 2000) in view of Neuman et al (Mol. Cell Biol. 14(10): 6607-6615, 1994; *of record in IDS), Hsiao et al (Genes & Development 8:1526-1537, 1994; *of record in IDS) and Jaenisch (Science 240: 1468-1474, 1988), as evidenced by Muller et al (J. Biol. Chem. 274(16):11220-11228, 1999) and DiLella et al (N.A.R. 16(9):4159, 1988) **is withdrawn** in preference for the new rejection set forth below.

10. **Claims 1-2, 4-6, 8, 11 and 13 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Muller et al (2000; *of record) in view of Muller et al (1999; *of record) Neuman et al (1994; *of record in IDS), Jaenisch (1988; *of record) and DiLella et al (1988; *of record).

This is a new rejection for the inclusion of Claims 1-2, 8, 11 and 13 into the rejection.

Muller et al teach a transgenic mammal comprising a recombinant nucleic acid molecule stably integrated into the genome of said mammal, said recombinant nucleic acid molecule comprising a cyclin A1 promoter operably linked to a nucleic acid encoding a bioluminescent protein, specifically GFP (pg 3317, col. 1, ¶2).

Muller et al do not teach *ipsis verbis* that the 1,444 bp (-1299 to +145) fragment of the human cyclin A1 promoter is an E2F-responsive promoter, or that it comprises E2F-binding sites. However, Muller cites the prior teaching of Muller et al (1999), wherein it is taught that this fragment does comprise at least two E2F binding sites (pg 11223, col. 2, Binding Sites). Absent evidence to the contrary, such is capable of binding an E2F1 polypeptide and is an E2F-responsive promoter (specification, pg 12, line 19).

Muller et al teach that the promoter activity results in increased production of the bioluminescent protein (e.g. pg 3323, Figure 6). Muller et al do not teach explicitly that the increased activity is due to E2F-binding to the E2F-responsive promoter. However, "Products of identical chemical composition can not have mutual exclusive properties." A compound and its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705,709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP §2112.01. In the instant case, the cyclin A1 promoter comprises E2F-binding sites, and its activity increases expression of the reporter gene. Thus, absent evidence to the contrary, the endogenous E2F1 is capable of binding to the E2F-responsive promoter to increase production of

the reporter protein. The burden is shifted to the Applicant to show that the prior art cyclin A1 promoter comprising E2F-binding sites does not possess the same properties as the instantly claimed promoter comprising E2F-binding sites.

Muller et al teach the isolation of germ cells from the transgenic animal (pg 3323, Figure 6; pg 3323, col. 1; pg 3324, Figure 8), as well as bone marrow cells (pg 3323, col. 2; pg 3325, Figure 9), which reasonably embraces stem cells, precursor cells and progenitor cells because those of ordinary skill in the art recognize that the bone marrow comprises said cell types (specification, pg 19, line 17).

Muller et al teach a method of making a transgenic mouse by standard techniques, the method comprising injecting recombinant DNA into the pronuclei of fertilized egg cells (pg 3317, col. 1, Generation of Transgenic Mice).

Muller et al do not teach the bioluminescent protein operably linked to the cyclin A1 promoter in the transgenic mouse is a luciferase. However, Muller et al does teach isolated transgenic mammalian cells comprising the cyclin A1 promoter operably linked to a bioluminescent protein, specifically luciferase (pg 3317, col. 2, Luciferase Assay).

Muller et al do not teach:
i) the E2F-responsive promoter is a human E2F-1 promoter; and
ii) the E2F-responsive promoter comprises SEQ ID NO:1.

However, at the time of the invention, Neuman et al taught a transgenic mammalian cell comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein, specifically luciferase (pg 6608, col. 2; pg 6609, col. 2, Results), wherein said E2F-responsive promoter is obtained from the human E2F1 promoter (pg 6608, col. 1, Genomic Cloning) that comprises a nucleic acid sequence that is 100% identical to SEQ ID NO:1 (complete sequence search results available in SCORE).

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Query Match             100.0%;  Score 269;  DB 5;  Length 362;
Best Local Similarity   100.0%;  Pred. No. 1.4e-60;
Matches  269;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 GGTACCATCCGGACAAAGCCTGCGCGCGCCCCCGCCCCCGCCATTGGCCGTACCGCCCCGCG 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     20 GGTACCATCCGGACAAAGCCTGCGCGCGCCCCGCCCCCGCCATTGGCCGTACCGCCCCGCG 79

Qy     61 CCGCCGCCCCCATCTCGCCCCCTCGCCGCCGGGTCCGGCGCGTTAAAGCCAATAGGAACCGC 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     80 CCGCCGCCCCCATCTCGCCCCTCGCCGCCGGGTCCGGCGCGTTAAAGCCAATAGGAACCGC 139

Qy    121 CGCCGTTGTTCCCGTCACGGCCGGGGCAGCCAATTGTGGCGGCGCTCGGCGGCTCGTGGC 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    140 CGCCGTTGTTCCCGTCACGGCCGGGGCAGCCAATTGTGGCGGCGCTCGGCGGCTCGTGGC 199

Qy    181 TCTTTCGCGGCAAAAAGGATTTGGCGCGTAAAAGTGGCCGGGACTTTGCAGGCAGCGGCG 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db    200 TCTTTCGCGGCAAAAAGGATTTGGCGCGTAAAAGTGGCCGGGACTTTGCAGGCAGCGGCG 259

Qy    241 GCCGGGGGCGGAGCGGGATCGAGCCCTCG 269
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Db   260 GCCGGGGGCGGAGCGGGATCGAGCCCTCG 288
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Neither Muller et al, Neuman et al nor Hsiao et al teach the method of making the transgenic mouse to comprise introducing the recombinant nucleic acid into an embryonic cell. However, at the time of the invention, Jaenisch taught that the ordinary artisan may predictably and successfully make transgenic mice by method steps such as introducing DNA into a pronucleus or embryonic stem cells (see entire paper).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology and the creation of transgenic cells and organisms. Therefore, the level of ordinary skill in this art is high.

Neither Muller et al, Neuman et al nor Jaenisch teach a transgenic mouse comprising a luciferase reporter operably linked to a promoter of interest. However, at the time of the invention, those of ordinary skill in the art had long known that one can successfully make a transgenic mouse comprising a luciferase reporter operably linked to a promoter of interest, wherein the luciferase will predictably "report" promoter activity in the transgenic mammal, as evidenced by DiLella et al.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first E2F-responsive promoter as taught by Muller et al with a second E2F-responsive promoter as taught by Neuman et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the E2F-responsive promoter as taught by Muller et al and the E2F-responsive promoter as taught by Neuman et al are both art-recognized E2F-responsive promoters, and thus equivalent in their ability to "report" E2F activity as per E2F binding to the E2F binding sites in the respective promoters. An artisan would be motivated to substitute a first E2F-responsive promoter as taught by Muller et al with a second E2F-responsive promoter as taught by Neuman et al because the E2F-responsive promoter of Neuman et al comprises a different set of transcription factor binding sites than the E2F-responsive promoter of Muller et al, and thus may yield a different tissue-specific pattern of expression than that observed for the E2F-responsive cyclin A1 promoter. Furthermore, Neuman et al teach that *in vitro* transfection experiments prohibit the determination whether E2F-1, -2, or -3 interacts with the E2F-1

promoter under physiological conditions because binding site preference differences *in vivo* between E2F family members might be obscured if they were over-produced *in vitro* (pg 6613, col. 1), thereby suggesting the production of a transgenic mammal so as to solve the problem.

It also would have been obvious to one of ordinary skill in the art to substitute a first bioluminescent reporter protein such as GFP as taught by Muller et al with a second bioluminescent reporter protein such as luciferase as taught by Neuman et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, those of ordinary skill in the art had long-recognized that bioluminescent proteins such as GFP and luciferase are functional equivalents as "reporter molecules" and readily substitutable, as successfully demonstrated by Muller et al regarding the cyclin A1 promoter operably linked to a bioluminescent protein, specifically GFP, and the cyclin A1 promoter operably linked to a bioluminescent protein, specifically luciferase. An artisan would be motivated to substitute a first bioluminescent reporter protein such as GFP with a second bioluminescent reporter protein such as luciferase because the art uses different standardized assays by which the ordinary artisan can quantify the amount of bioluminescent reporter activity in a given *in vitro* or *in vivo* system, and such is but an experimental design choice by the artisan.

It also would have been obvious to one of ordinary skill in the art to substitute a first method of making a transgenic mammal as taught by Muller et al with a second method of making a transgenic mammal as taught by Jaenisch with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute a first method of making a transgenic mammal as taught by Muller et al with a second method of making a transgenic mammal as taught by Jaenisch because introducing recombinant DNA into an embryonic cell and/or and egg cell, e.g. pronuclear injection, have long been recognized in the art to predictably succeed in producing transgenic mice, and as such the functionally equivalent methods of making transgenic mammals are but design choices for the artisan.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that Muller (1) does not teach or suggest a transgenic mouse having a recombinant nucleic acid molecule stably integrated into the genome of the mouse, wherein the recombinant nucleic acid molecule comprising an E2F responsive promoter is operably linked to a nucleic acid encoding a bioluminescent protein. Neuman, Jaenisch, Muller (2) and DiLella each fail to cure the deficiencies in the teachings of Muller.

Applicant's argument(s) has been fully considered, but is not persuasive. Muller (1) teach a transgenic mouse comprising a recombinant nucleic acid molecule stably integrated into the genome of said mouse, said recombinant nucleic acid molecule comprising a cyclin A1 promoter operably linked to a nucleic acid encoding a bioluminescent protein, specifically GFP. Muller (1) do not teach *ipsis verbis* that the human cyclin A1 promoter is an E2F-responsive promoter, or that it comprises E2F-binding sites. However, Muller (1) cites the prior teaching of Muller (2), wherein it is taught that this fragment does comprise at least two E2F binding sites. Absent evidence to the contrary, such is capable of binding an E2F1 polypeptide and is an E2F-responsive promoter.

Muller (1) teach that the promoter activity results in increased production of the bioluminescent protein. Muller (1) do not teach explicitly that the increased activity is due to E2F-binding to the E2F-responsive promoter. However, "Products of identical chemical composition can not have mutual exclusive properties." A compound and its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705,709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP §2112.01. In the instant case, the cyclin A1 promoter comprises E2F-binding sites, and its activity increases expression of the reporter gene. Thus, absent evidence to the contrary, the endogenous E2F1 is capable of binding to the E2F-responsive promoter to increase production of the reporter protein. The burden is shifted to the Applicant to show that the prior art cyclin A1 promoter comprising E2F-binding sites does not possess the same properties as the instantly claimed promoter comprising E2F-binding sites.

Applicant argues that nothing in Neuman teaches or suggests the specifically recited mouse of claim 1.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Muller (1) taught a transgenic mouse comprising a recombinant nucleic acid molecule stably integrated into the genome of said mouse, said recombinant nucleic acid molecule comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein. Neuman et al taught a transgenic mammalian cell comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein, specifically luciferase, wherein said E2F-responsive promoter is obtained from the human E2F1 promoter that comprises a nucleic acid sequence that is 100% identical to SEQ ID NO:1.

Applicant argues that there is no objective reason provided in any of the cited references, alone or in combination, which would lead the skilled artisan to arrive at the claimed invention. Moreover, there is no evidence that the results generated by combining and/or modifying these references would have been predictable at the time the instant invention was made.

Applicant's argument(s) has been fully considered, but is not persuasive. It is unclear what element of the instantly claimed invention would have been unpredictable at the time of the instantly asserted invention in light of the prior art-recognized ability for the routineer to make a transgenic mouse comprising a recombinant nucleic acid molecule stably integrated into the genome of said mouse, said recombinant nucleic acid molecule comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein (Muller (1), Jaenisch), and in light of the prior art successfully demonstrating the ability of a human E2F1 promoter that comprises a nucleic acid sequence that is 100% identical to SEQ ID NO:1 operably linked to a nucleic acid encoding a bioluminescent protein, specifically luciferase (Neuman). The E2F-responsive promoter as taught by Muller (1) and the E2F-responsive promoter as taught by Neuman et al are both prior art-recognized E2F-responsive promoters, and

thus equivalent in their ability to "report" E2F activity as per E2F binding to the E2F binding sites in the respective promoters. Furthermore, at the time of the instantly asserted invention, those of ordinary skill in the art had long known that one can successfully make a transgenic mouse comprising a luciferase reporter operably linked to a promoter of interest, wherein the luciferase will predictably "report" promoter activity in the transgenic mammal (DiLella).

Applicant argues that any suggestion that it would have been obvious to replace the promoter taught by Muller and Neuman is an improper application of hindsight based on Applicants' disclosure in the instant application.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the instant case, Muller (1) taught a transgenic mouse comprising a recombinant nucleic acid molecule stably integrated into the genome of said mouse, said recombinant nucleic acid molecule comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein. Neuman et al taught a transgenic mammalian cell comprising an E2F-responsive promoter operably linked to a nucleic acid encoding a bioluminescent protein, specifically luciferase, wherein said E2F-responsive promoter is obtained from the human E2F1 promoter that comprises a nucleic acid sequence that is 100% identical to SEQ ID NO:1. Jaenisch taught methods of making transgenic mice.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633

/Joseph T. Woitach/
Supervisory Patent Examiner, Art Unit 1633